THE INFLUENCE OF QUININE AND SOME ANTIPYRETICS ON METABOLISM

BY

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I HEREBY RECOMMEND THAT THE THESIS PREPARED UNDER MY SUPERVISION BY William Lionel McClure

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Introduction

Quinine is one of the drugs which have been known to medicine since a very remote period and still holds a unique position in therapeutics. The earliest definite knowledge of its remedial properties is recounted in the case of the Countess d'El Chinchon, wife of the viceroy of Peru. She was attacked by an intermittent fever in the year 1638 and a corregidor of Loxa recommended the use of a powder which cured her. In 1640 she brought some of the powder to Europe and distributed it among her friends whence it received the name of Poudre de la Comtesse. The name of this prominent woman of her time has been perpetuated in the cinchonas due to the efficacy of these substances in her illness. La Poudre de la Comtesse was introduced widely by the Jesuits of Rome and became known in some sections as the Jesuits powder. Louis XIV was cured of an obstinate, intermittent fever in 1679 by a secret remedy given to him by an English charlatan named Talbot. The king purchased the secret for a large sum of money and an annuity and commanded the publishing of the name of this wonderful cure, which was nothing other than a strong vinous solution of cinchona, for the public good. Joseph Jessieu who was sent to America in 1735 stated that the antipyretic properties of Peruvian bark were first known to the Indians. Sydenham and Torti were first to formulate the rules for systematic and proper employment of powdered cinchona in treatment of malarial fever. Pelletier and Caventon in 1820 rendered a very important service to therapeutics in submitting the bark to the analytical procedures which had been applied earlier to opium. Up to the time of this work the use of powdered

cinchona was attended by two serious drawbacks - the difficulty in administering large enough doses to be effective, and the slowness of absorption.

Perhaps the most striking example in modern medicine of a specific in the truest sense is the employment of quinine in the treatment of malarial fevers. This statement is easily attested by watching the action of quinine salts on the hematazoa in a drop of malarial blood, and by the fact that quinine has little if any effect as an antipyretic in the normal, healthy organism or in other types of fevers. Due to the efficacy of this drug in cases of malaria it very early became popular as a remedy for febrile conditions in general. Its place of former importance in this respect has been usurped by the more modern and effecient antipyretics discovered about the middle of the ninteenth century.

The discovery of pharmacological agents and their introduction into medicine has come, in many if not a majority of cases, quite by accident. The extensive use of these substances in therapeutics is, of course, always a stimulus for an enormous amount of research in an attempt to bring to light the fundamental reasons for their physiological action as well as the scope of this action. This has been quite true in the case of quinine. The analytical work of Pelletier and Caventon in 1820 was followed by numerous physiological investigations beginning about the middle of the ninteenth century and pursued with marked intensity to about 1890. The researches were chiefly the work of German scientists or at least the products of German laboratories. It is a notable fact that some of the earlier experiments led to results of a doubtful intrepretation and in some cases to quite contrary conclusions.

This statement is made with particular reference to the effects of quinine on the nitrogenous metabolism. On this phase of the question the later studies have led to more concordant results but the work has not been so prolific but that it would seem to admit of further confirmation. This statement seems especially true when viewed in the light of the profound effects observed by investigators on some phases of the nitrogenous metabolism, particularly the uric acid excretion in man.

Researches have established the fact that quinine, unlike most other important alkaloids, does not effect specialized forms of tissue or living matter alone but seems to act on almost all forms of protoplasm. This fact was established chiefly by the observations of various workers on undifferentiated protoplasm; O. and R. Hertwig on the reproductive cells of animals; Binz on the amoeba; Darwin on the vegetable cell. Quinine in small amounts seems to stimulate the movements of the amoeba at first but larger quantities paralyze this organism immediately and the protoplasm assumes a dark, granular appearance. The action of this drug is said to be a general nutritive effect on almost all forms of living matter and is cited to show the unique position of quinine in this respect. While strychnine and some other alkaloids have much the same general nutritional action attributed to them yet it must be remembered that they also exert a very profound influence on some special form of tissue which prevents or interferes with the study of this property in the higher animals. From these considerations it is readily seen how quinine has acquired the name of a a protoplasm poison whereas the marked effect of strychnine on the nerve cell causes it to be classed among nerve poisons, although

in organisms devoid of a nervous system it resembles quinine in its effects. This widespread action of quinine on living matter undoubtedly explains much of the interest and exhaustive inquiry into the influence of the drug on the metabolic processes in the human organism.

Keeping pace with and contributory to the late, rapid progress of the knowledge of metabolism and physiological phenomena has been the development of many analytical microchemical methods which lend themselves more conveniently and accurately to the study of biological problems than those methods at the disposal of the earlier investigators.

In view of the abovementioned considerations it has seemed worth while to undertake a further study of the effects of quinine on metabolism with particular reference to its influence on the nitrogen excretion.

The Literature

The literature on this question is so voluminous that it is hardly justifiable to proceed to a delineation of the results of these experiments without reviewing the work of former investigators in the field.

Probably the first research on the influence of medicinal drugs on metabolism was that of H. Ranke(1). The phase of his work which is of particular interest in this connection is the study of the effect of the administration of quinine sulfate upon the uric acid excretion of healthy men. These experiments were carried out upon himself and eight other persons. A mixed diet was fed in each case. To the first three subjects was given the same amount of each article of food daily while the others were allowed to eat

according to their appetites and pleasure but the kind of food remained the same. The uric acid was determined from twenty four hour specimens of urine. Four of these tests showed an average decrease in the uric acid elimination of about 50%.

(1) From 0.648 to 0.271

(2) From 0.519 to 0.395

(3) From 0.603 to 0.315

(4) From 0.659 to 0.372

In the other experiments also, with the exception of the sixth in which Ranke developed a diarrhea, there was a considerable decrease. The results of the observations on the urea excretion were very inconstant if not quite diverse leading to the criticism by Prior; "jedenfalls ist Vieles ausser Acht gelassen, auf welches man sein Augenmerk hätte richten müssen."

W.A. Hammond(2) observed that on the day of ingestion of quinine and the day thereafter an increase in the excretion of urea but a decrease in the uric acid. The author's observations were made upon himself and his results may be justly criticized on the ground that he was ill of an "Intermittens tertiana" and hence not in a normal condition.

The contributions of F.H. Redenbacher(3) are not entirely trustworthy since there was an insufficient control of the diet. He found always an increase in the urea excretion.

H.V. Bosse(4) worked on this question under the direction of Buchheim experimenting on a healthy man fifty years of age. His results seem open to criticism on the ground of insufficient control. He observed in two experiments an average decrease of 90% in the uric acid excretion.

Unruh(5) undertook a study of the effects of quinine on non-febrile and febrile individuals. His observations on the first class were made on two men afflicted with syphilis. In both patients he found at first a slight increase in the urea excretion followed by a diminution. In his conclusion he attempts to stretch the findings in these cases to cover non-febrile conditions in general to which protest must be made for certainly a syphilitic individual is not in a state of health. In any event his conclusions are far from certain stating that quinine not always but in all probability frequently depresses the metabolism in non-febrile conditions. The chief result of his observations on febrile patients is that in quinine we do not have an absolutely certain antipyretic.

Binz(6) in explanation of the above widely divergent results points out that under pathological conditions the stomach does not contain free hydrochloric acid in sufficient amounts to properly effect the solution of the quinine thus hindering the absorption.

G. Kerner(7) in a series of brilliant and conclusive experiments on himself studied the effects of both large and small doses of quinine. He noted a decrease in the nitrogen excreted which was proportional to the dose taken. Upon the ingestion of 0.6 gr. quinine hydrochloride the nitrogen fell from 18.334 gr. to 16.170 gr. and after 1.66 gr. of the drug the excretion fell to 13.979 a rather profound effect. He was probably the first to advance the suggestion that an inhibition in the formation and not in the excretion of the products of metabolism had occurred.

Von Boeck(8) made an interesting observation on dogs

in which he had maintained a nitrogenous equilibrium before the administration of 1.0 gr. quinine sulfate. During the quinine series of five days a total of 9.72 gr. less of nitrogen was excreted than was contained in the food taken. Von Boeck further noted that this effect continued for three days and concluded in accord with Kerner that though most of the quinine was excreted in twenty four hours some part remained in the body longer. To ascertain whether or not this effect was due to lack of absorption in the intestine he conducted a series of experiments in which the feces were carefully measured both with and without the administration of quinine. Since there was no increase in the feces after the ingestion of quinine the conclusion was that there was no decreased absorption in the intestine. This procedure is open to the criticism that constant weights of the feces even on a weighed diet does not necessarily imply a constant elimination of fecal nitrogen. The results of von Boeck's observations, however, under the conditions in which they were made could not reasonably be accounted for by variation in the fecal nitrogen.

A. Schulte(9) working under the direction of Zuntz noted in the latter, after taking at short intervals in three doses 1.8 gr. quinine hydrochloride, a decrease of 39% in the urea excreted. This result was taken from the average of three normal days and four following days.

Jansen(10) was unable to convince himself of a decrease in the uric acid excretion under the influence of quinine and what is more he observed in fowls an increase.

Jerusalimsky(11) in the laboratory of Professor Salkowski after noting a diminution of the nitrogenous constituents in human

excreta upon the administration of quinine sought the explanation not in the effect of quinine upon the function of the cells but upon the lowering of the blood pressure.

Johannson(12) concluded that the explanation for the temperature lowering by cinchonin was to be sought in its depressing effect on metabolism. The decrease showed itself in much smaller quantities of urea excreted in man, the dog and the cat. He noted a decrease of 24,8% in urea and 64.1% in uric acid after the ingestion of 0.5 gr., 1.0 gr. and 1.5 gr cinchonin sulfate by a healthy man weighing 60 kilos on a constant diet.

Bauer and Kunstle(13) in experiments on febrile patients came to divergent results. They emphasize, however, that through their researches it was established that by large doses of quinine the protein katabolism was retarded.

H. Oppenheim(14) under the direction of Zuntz carried on some investigations with himself as the subject. In two tests he took at short intervals 1.0 gr. quinine. In one case the urea excretion exceeded the normal figure by about 4.0 gr. without marked increase in the urine volume. In the next twenty four hours the figure sank back to normal again. In the second instance an increase of 4.52 gr. in the urea was observed. When the average figures are calculated the results show about 11.5% increase in one case and 16.8% in the other.

It seems quite evident from the experimental evidence presented thus far that the influence of quinine on the nitrogenous metabolism was yet an open question. It was at about this point that Prior(15) published the findings of a brilliant and painstaking series of researches undertaken in an attempt to bridge or wipe

out the hiatus existing between the results of former investigators. He chose himself as experimental subject in order to avoid any error that might arise due to inability to control all factors in another. The periods of observation were from 7:00 A.M. to the same hour on the following day and a constant diet was taken at the same hours each day. Urea was determined by the method of Pflüger; uric acid by the method of Salkowski; nitrogen by the Will-Varrentrap method. The fecal nitrogen was determined each day. After the establishment of nitrogen equilibrium quinine hydrochloride was ingested in doses of various sizes. The following table gives a concise resume of the results of all these tests.

Averages	Urine Volume	Urea	Uric acid	N in feces
The normal urine	1586	39.76	0.74	0.67
(1) After single doses of quinine, 1.5 gr.	1800	32.70	0.12	0.43
(2) After repeated large doses of quinine	1743	33.07	0.22	0.51
(3) After repeated small doses of quinine	1657	34.00	0.41	0.83
(4) After a single enormous dose, 4.0gr. (2 gr. at 7:00 A.M. and 2 gr. at 12:00 M.)	1820	28.10	0.07	0.93
Normal days at the close of the series	1580	39.60	0.74	0.94

These figures represent the following percentage changes in the composition of the urine under the above conditions.

Experiment	Increase in urine volume	Decrease in urea excretion	Decrease in uric acid excretion
(1)	13.49	17.76	83.78
(2)	9.90	16.83	70.27
(3)	4.48	14.49	44.59
(4)	14.75	29.33	90.54

Without respect to the size of the dose the average percentage changes are; (1) increase in the urine volume of 10.65%; (2) decrease in urea excretion of 19.60%; (3) decrease in uric acid excretion of 72.29%.

The principal conclusions which Prior draws from these observations are; (1) in quinine we have a powerful medium for inhibiting the katabolic changes of protein substances in the living organism; (2) the diminution in the amounts of these end products excreted is not due to a depression in the excretion itself but to a retarding influence on their formation; (3) the effects observed are in proportion to the size of the dose taken. Probably the chief criticism which might be directed against this work is the fact that during the tests the subject lived on a mixed and not a purine free diet which is generally considered necessary where a true picture of the endogenous uric acid excretion is desired.

In order to determine the influence of quinine on the metabolic processes of the starving organism Prior carried out some experiments on a dog starved to the point of constant nitrogen excretion. Observations on urea are the only determinations of nitrogenous products recorded and the results confirm those of the first work.

About the time of Prior's work Sassetzky(16) published his findings on the effects of quinine on metabolism as observed upon its administration to fourteen typhus patients. His results are in harmony with those of Prior.

Livierato(17) in a research on the effects of the common antipyretics on metabolism noted a decrease in the urea excretion under the influence of quinine.

Venediger(18) in a "selbstversuche" found that upon the ingestion of 2.0 gr. quinine the nitrogen excretion fell in one case from 12.17 gr. to 10.71 gr. and in another case from 12.23 gr. to 10.59 gr.

Von Noorden and Zuntz(19) in 1894 still regarded the quinine question as unsettled, vouched for in the statement by Hr. von Noorden that "uber die Einwirkung des Chinins auf den menschlichen Stoffwechsel zwar schon zahlreichende Arbeiten ausgefuhrt seien, aber die Resultate widersprechen sich untereinander." In "selbstversuche von Dr. Irisawa" these investigators noted a slight preliminary rise in the nitrogen excretion upon the administration of quinine followed by a fall of about the magnitude observed by Prior which effect lasted for two days in the after period. The nitrogen then came back to normal. The uric acid, determined after the method of Ludwig-Salkowski, amounted to 0.7 - 0.95 gr. in the fore period, 0.75 - 0.87 gr. in the quinine period; on the first day of the after period it sank to 0.5 - 0.58 gr. daily and later rose to 0.76 gr.

An interesting observation was made by Daniel(20) in 1898. Upon the administration of 3.0 gr. quinine two days before the ingestion of 500 gr. thymus the excess excretion of uric acid which

should have been noted under these conditions was suppressed almost entirely. He states that this effect on the uric acid elimination is in harmony with the action of quinine in producing leukocyte disintegration.

A recent investigation by Riddle and Anderson(21) in which they used doves for experimentation has shown that under the influence of small doses of quinine sulfate the total size of the eggs produced by these birds is much decreased and that the decrease in the yolk and albumin is marked.

The researches of the later workers on this question seem to be in pretty fair agreement in so far as the urea and total nitrogen excretion are concerned. It should perhaps be stated that all metabolic changes are not affected by quinine. The energy metabolism of the body seems to be unaffected under its influence for the respiratory quotient remains practically unaltered and hence it can not be assumed that oxidation in the tissues undergoes any change. With reference to the effects of quinine on the uric acid metabolism it seems that more data are desirable especially in view of the profound changes observed by Prior. Nowhere in the literature was there found any investigation on the influence of quinine on creatinine excretion.

Experimental Methods and Data

(a) The analytical methods used

Throughout the entire work the following analytical methods were used; hydrogen ion concentration by the indicator method (Henderson and Palmer's adaptation of Sorenson's method); the Folin method for acidity by titration; creatinine by the Folin micrcolorimetric method; uric acid by the microchemical method

(Benedict and Hitchcock modification); urea according to the Van Slyke and Cullen procedure based on Marshall's urease method; ammonia by the same technic omitting, of course, the addition of the enzyme and using 5 cc. of undiluted urine; total nitrogen by the Kjeldahl method.

The quinine hydrochloride, which was used in all save two experiments, was prepared in the laboratory by saturating a concentrated alcoholic solution of the alkaloid with hydrochloric acid, evaporating on the water bath to remove excess acid, redissolving the residue in alcohol and precipitating withether. A very pure product was obtained.

(b) Hour to hour metabolism studies

The first series of experiments were hour to hour metabolism studies undertaken more especially for the purpose of observing the effects of quinine on the hourly elimination of uric acid and creatinine as it is well known that this drug is qualitatively detectable in the urine very soon, usually about thirty minutes, after its ingestion. The subject, W.L.Mc., was a healthy man 25 years of age and weighing 60 kilos. The diet was purine free throughout each test as was the evening meal before each series was begun. No breakfast was taken on the days of observation in order to secure as little variation as possible in the hour to hour elimination of endogenous uric acid. To insure a good workable volume of urine and to minimize errors which might be introduced through incomplete voiding, 200 cc. of water were taken every hour. The bladder was emptied as completely as possible at 7:00 A.M. and the urine collected in hourly specimens thereafter.

Tables 1 to V11 contain the results of three such studies.

Table 1

The following observations were taken on a single quinine day, 0.5 gr. of the drug(alkaloid) having been swallowed in a capsule at 9:00 A.M.

Period	Urine volume	P_H	Titratable acidity cc.	Creatinine mg.	Uric acid mg.
(A.M.)					
7:00-8:00	50	6.23	12.38	74.0	31.5
8:00-9:00	55	6.63	7.7	88.0	32.45
9:00-10:00	160	7.0	7.8	80.0	29.9
10:00-11:00	195	7.4	5.0	68.0	30.6
11:00-12:00	140	7.4	4.2	65.8	30.3
(P.M.)					
12:00-1:00	225	7.4	8.1	67.5	31.0
1:00-2:00	65	7.4	8.1	67.6	37.3
* 2:00-3:00	303	6.63	12.9	75.7	31.8
3:00-4:00	105			71.4	30.1

* At this point a lunch consisting of rolled oats, two eggs, a slice of toast and an orange was taken. This may account for the sudden rise in the uric acid the following hour.

In view of the following experiments it is believed that the above variations in the creatinine elimination are within the normal limits.

In tables 11, 111, and 1V are presented the results of the second hour to hour metabolism study. In this series the quinine day was preceded and followed by a normal day and 1.0 gr. quinine(alkaloid) was ingested at 9:00 A.M. on the quinine day. In all other respects the conditions were essentially the same as in the first experiment.

Table 11
Normal day

Period	Urine volume	P_H	Titratable acidity cc.	Creatinine mg.	Uric acid mg.
(A.M.)					
7:00-8:00	50	6.23	21.5	74.0	24.0
8:00-9:00	60	6.23	18.9	81.6	26.4
9:00-10:00	300	7.0	12.6	81.6	28.8
10:00-11:00	95	7.4	5.2	68.4	23.7
11:00-12:00	360	7.4	10.8	77.0	23.4
(P.M.)					
12:00-1:00	190	7.4	7.2	64.6	21.2
* 1:00-2:00	90	7.4+	1.1	73.8	25.2
2:00-3:00	250	7.0	8.5	75.0	22.2

*Lunch

Table 111
1.0 gr. quinine(alkaloid)
at 9:00 A.M.

Period	Urine volume	P_H	Titratable acidity cc.	Creatinine mg.	Uric acid mg.
(A.M.)					
7:00-8:00	35	5.92	27.3	70.7	37.4*
8:00-9:00	60	5.92	17.5	74.4	42.1*
9:00-10:00	180	6.63	14.4	64.2	20.3
10:00-11:00	110	7.4	4.0	57.8	22.1
11:00-12:00	40	7.0	6.0	57.1	24.3
(P.M.)					
12:00-1:00	240	6.63	13.9	56.6	20.0
1:00-2:00	95	6.23	19.3	57.3	28.5
2:00-3:00	200	6.63	20.0	55.0	25.0

*In view of the diet control these high figures for uric acid are unexplainable except that undoubtedly the samples taken for analysis were too large to be within the limits of accuracy of the method. It is regrettable that duplicates were not saved.

Table lV
Normal day

Period	Urine volume	PH	Titratable acidity cc.	Creatinine mg.	Uric acid mg.
(A.M.)					
7:00-8:00	50	6.63	10.2	79.0	22.3
8:00-9:00	40	5.92	11.0	92.0	27.0
9:00-10:00	110	6.63	4.1	82.5	26.4
10:00-11:00	160	7.0	5.4	72.4	23.5
11:00-12:00	190	6.63	12.5	76.3	25.0
(P.M.)					
12:00-1:00	35	6.23	15.4	65.4	16.2*
1:00-2:00	55	6.63	8.8	92.4	34.3
2:00-3:00	350	6.63	7.0	88.9	23.8

*This sudden variation in the uric acid excretion is not accounted for except by the irregularities in the volumes of urine between 1:00 P.M. and 3:00 P.M.

The results of the third study in hour to hour excretion are presented in tables V, Vl, and Vll. The details of this experiment are the same as the preceding one except that 1.0 gr. quinine hydrochloride instead of the alkaloid was ingested at 9:00 A.M. on the second day.

Table V
Normal day

Period	Urine volume	PH	Titratable acidity cc.	Creatinine mg.	Uric acid mg.
(A.M.) 7:00-8:00	65	6.23	12.0	72.8	18.2
8:00-9:00	75	5.92	12.7	87.7	21.6
9:00-10;00	95	7.0	6.5	83.6	21.8
10:00-11:00	265	7.0	6.4	80.8	20.2
11:00-12:00	185	7.0	7.0	80.4	18.4
(P.M.) 12:00-1:00	100	7.4	6.4	80.6	19.1
* 1:00-2:00	90	7.4+	3.0	83.2	21.4
2:00-3:00	210	7.4	8.8	91.5	22.1
3:00-4:00	95	7.0	4.6	83.7	21.0

*Lunch

Table VI
1.0 gr. Q.HCl
at 9:00 A.M.

Period	Urine volume	PH	Titratable acidity cc.	Creatinine mg.	Uric acid mg.
(A.M.) 7:00-8:00	45	5.92	13.05	74.7	19.4
8:00-9:00	135	6.23	6.5	71.0	19.8
9:00-10;00	140	7.0	3.9	65.3	19.7
10:00-11:00	50	6.63	5.2	67.0	18.8
11:00-12:00	225	6.63	12.1	69.7	23.4*
(P.M.) 12:00-1:00	110	6.23	16.5	77.7	26.7
1:00-2:00	255	6.63	15.0	72.1	22.8
2:00 -3:00	155	6.63	19.2	81.5	28.1
3:00 -4:00	135	6.63	18.9	67.5	24.2

* Due to the fatigue to the eyes entailed on frequent

reading of the colorimeter from this point on readings were made

on the reverse cup. Theoretically no difference should occur from this procedure however some visual error may have been introduced.

No lunch taken on this day.

Table V11
Normal day

Period	Urine volume	PH	Titratable acidity cc.	Creatinine mg.	Uric acid mg.
(A.M.)					
7:00-8:00	15	6.23		56.3	16.9
8:00-9:00	20	5.93		88.3	22.6
9:00-10:00	25	6.63		83.3	25.2
10:00-11:00	25	6.63		64.7	19.5
11:00-12:00	25	6.63		68.2	19.2
(P.M.)					
12:00-1:00	70	6.63		82.0	21.0
* 1:00-2:00	40	6.23		88.3	25.4
2:00-3:00	90	6.23		84.8	23.6
3:00-4:00	165	6.63		82.5	23.6

*Lunch

A study of the figures presented in the foregoing experiments adduces the following conclusions;

(1) The hydrogen ion concentration of the urine seems to remain unchanged or rather varies in the same manner on normal and quinine days indicating that the quinine produces no effect on the true acidity of the urine studied from the standpoint of hour to hour elimination. This statement is also borne out generally by the figyres on the titratable acidity.

(2) The hour to hour elimination of uric acid is apparently unaffected within the first five or six hours after the administration of quinine although other investigators have shown that the drug usually appears in the urine within thirty minutes after its ingestion.

(3) Quinine likewise seems to exercise no effect on the hourly elimination of creatinine.

(c) General or twenty four hour metabolism studies

In table V11 are contained the results of a metabolism study of a succession of normal and quinine days. The subject, W.L.Mc. was a healthy man twenty five years of age and weighing about 60 kilos. The diet throughout the experiment was purine free and the constituents are indicated below. Quinine hydrochloride was taken on the days and in the amounts indicated in the table. The 1.0 gr. dose was divided into two parts, the 1.5 gr. and 2.0 gr. doses into three parts and taken at intervals of three to four hours during the day beginning about 8:00 A.M. The urine was collected between the hours of 7:00 A.M. and 7:00A.M. and each twenty four hour specimen analysed for the constituents indicated.

Date	Urine volume	PH	Titratable acidity cc.	Creatinine gr.	Uric acid gr.	Urea N gr.	Urea N %	Ammonia N gr.	Total N gr.
April 1	1150	7.0	220	1.69	0.40	9.77	88.8	0.39	10.99
April 2	1080	7.0	190	1.90	0.40	10.17	87.5	0.36	11.62
April 3	1200	7.0	223	1.84	0.54	10.22	88.5	0.40	11.54
*April 4	1010	7.0	190	1.72	0.46	9.39	86.4	0.32	10.86
#April 5	1010	7.0	181	2.04	0.66	8.91	85.7	0.28	10.39
April 6	760	7.0	181	1.99	0.45	7.98	85.4	0.41	9.34
April 7	1100	6.63	266	1.94	0.39	8.10	84.3	0.41	9.61
April 8	1410	7.0	245	1.97	0.49	10.08	88.0	0.38	11.45
°April 9	1570	7.0	188	2.04	0.69	9.33	86.7	0.34	10.76
April 10	1145	7.0	174	1.90	0.57	7.76	84.1	0.43	9.22
April 11	1140	6.63	255	2.01	0.48	8.00	83.9	0.41	9.53
April 12	1220	6.63	234	1.92	0.50	8.23	85.5	0.44	9.62

*1.0 gr. Quinine HCl divided into two doses and taken at 8:00 A.M. and 12:00 A.M.

#1.5 gr. Quinine HCl divided into three doses and taken at intervals of four hours beginning at 8:00 A.M.

°2.0 gr. Quinine HCl divided into three doses and taken at intervals of four hours beginning at 8:00 A.M.

Daily diet

Breakfast		Dinner		Supper	
Shredded Wheat	30 gr.	Shredded Wheat	30 gr.	Potato	150 gr.
Banana	80 "	Banana	80 "	Beans, bkd.	150 "
Sugar	15 "	Sugar	15 "	Bread	50 "
Milk	100 cc.	Milk	100 cc.	Butter	10 "
Bacon	15 gr.	Potato	150 gr.	Apples (stewed)	150
Toast	30 "	Toast	30 "		
Butter	10 "	Butter	10 "		

Table IX contains the figures for an experiment similiar to that represented by table VIII. The subject, H.B.L., was a healthy man 31 years of age and weighing about 80 kilos. The two doses of quinine taken on the days indicated in the table were divided into three parts and taken at intervals of three to four hours beginning about 8:00 A.M.

It may be mentioned that in all these experiments on the quinine day and the day following when picric acid was added to the urine in the creatinine determination a yellowish precipitate clouded the liquid but dissolved on the addition of the 10% alkali. This reaction was rarely observed later than the first day after the ingestion of quinine*

*Hartman, H. and Zila, L., Arch. f. exp. Path. u. Pharm., 1918, LXXXIII, 221.

Date	Urine volume	P_H	Titratable acidity cc.	Creatinine gr.	Uric acid gr.	Urea N gr.	Urea N %	Ammonia N gr.	Total N gr.
May 8	1134	7.0	304	1.57	0.49	10.15	86.5	0.37	11.76
May 9	1040	6.63	336	1.76	0.51	10.56	85.5	0.36	12.34
May 10	960	6.23	388	1.76	0.51	10.20	86.0	0.44	11.88
*May 11	1550	6.23	432	1.80	0.46	10.55	86.7	0.45	12.14
°May 12	1270	6.63	272	1.72	0.47	9.42	86.2	0.34	10.94
May 13	1025	6.63	268	1.78	0.46	8.27	83.7	0.37	9.88
May 14	1166	6.63	320	1.72	0.46	9.38	85.3	0.38	10.98
May 15	1360	6.63	336	1.72	0.52	10.78	86.2	0.42	12.50
May 16	1242	6.63	344	1.72	0.45	9.69	86.0	0.39	11.28

*1.0 gr. quinine hydrochloride divided in two doses and taken three to four hours apart beginning at 8:00 A.M.

°1.5 gr. quinine hydrochloride divided into three doses and taken three to four hours apart beginning at 8:00 A.M.

The daily diet, purine free, was as follows:

Oleomargarine	75 gr.	2 eggs	Lettuce
Bread	275 "	Milk 50 cc.	French dressing
Potatoes	440		Two Shredded Wheat Biscuits
Cheese	40 "		Banana 90 gr.
Small slice fat bacon			Moderate dish rhubarb

In the two foregoing experiments the usual symptoms occurring upon the ingestion of large doses of quinine were manifested. In the latter a slight and not serious gastro-intestinal irritation was experienced.

A study of the figures presented in the two foregoing general metabolism studies on the effects of quinine on the nitrogenous metabolism in the healthy human organism lends confirmatory evidence to the results of the majority of former investigators in so far as the urea and total nitrogen excretion is concerned. The decrease in these constituents of the urine under the influence of quinine is of about the same magnitude as that observed by Prior and von Noorden and Zuntz, three comparatively recent and careful workers on this question.

In the first of the two preceding experiments it will be noted that there was a slight but probably not significant rise in the uric acid excretion after the administration of quinine. In the second there is practically no variation in the uric acid elimination and such as there is may hardly be regarded otherwise than that which might occur under normal conditions. These data then are not in agreement with the profound effects on the uric acid elimination under the influence of quinine which have been reported by some investigators. This is especially true when these results are compared with those of Prior in which he observed an average decrease in the uric acid excretion of 72.29%.

As was observed in the hour to hour metabolism studies the hydrogen ion concentration and the creatinine excretion seem to be unaffected by ingestion of quinine.

In an attempt to confirm in another species of mammal these findings on the nitrogen excretion a series of studies was carried out using rabbits as experimental animals. There was not found in the literature any instance in which quinine had been administered to rabbits for the purpose of noting its effect on the nitrogenous metabolism. The rabbits were confined in metabolism cages and were fed a daily ration consisting of 150 cc. milk and 10 gr. cane sugar, with the exception of one, which on the account of being of much greater weight, was given 200 cc. milk daily. In cases where the animals would not drink the ration was fed by stomach tube. The urine was expelled from the bladder by catheterization at the same hour every morning, added to that which had been voided by the animal and analysed for the constituents indicated in the following tables. As very little ammonia is excreted in rabbit urine urea and ammonia were determined together. That the diet contained sufficient nitrogen is evidenced by the fact that weight was maintained throughout the experiments and in most instances there was a slight gain. The doses of quinine hydrochloride were dissolved in 5 to 10 cc. water and given by stomach tube. In cases where the dose was divided it is indicated in the table. Tables X, Xl, Xll and Xlll contain the figures for observations on four different animals.

Table X

Date	Urine volume	P_H	Titratable acidity cc.	Creatinine gr.	Urea & NH_3 N gr.	Total N gr.	Body wt. kg.
4/18	110	5.92	59.5	0.10	0.74	0.87	2.1
4/19	103	5.45	64.5	0.11	0.77	0.90	2.1
4/20	150	5.92	60.0	0.11	0.89	0.92	2.09
4/21	160	5.92	61.0	0.10	0.78	0.89	2.0
*4/22	113	5.92	41.8	0.10	0.87	1.00	1.97
*4/23	110	alk. to phenolph.		0.09	0.64	0.80	1.97
#4/24							

*0.5 gr. quinine hydrochloride was given in a single dose on each of these days.

The animal died on this date. Symptoms of collapse and a rather marked diarrhea had developed. This latter fact due to which the urine was contaminated with feces probably accounts for the sudden change in reaction on the 23d. On autopsy the stomach was found greatly distended with undischarged contents. There was apparently a complete pyloric stenosis, the sphincter feeling almost as hard as a marble to the touch. There was a parasitic infection of the liver which had been observed in other animals coming from the same group as this one. Autopsy was performed immediately after death.

Table Xl.

Date	Urine vol.	P_H	Titrble ac. cc.	Creat. gr.	Urea & am. N gr.	Tot. N gr.	Body wt. kg.	Remarks
4/27	122	5.92	33.0	0.051	0.52	0.60	1.2	
4/28	100	5.92	32.0	0.054	0.43	0.50	1.2	
4/29	140	7.0#	26.0	0.053	0.55	0.63	1.16	
4/30	130	6.23	28.5	0.055	0.49	0.56	1.1	
5/1	116	6.63	26.0	0.054	0.56	0.64	1.15	0.3 gr.Q.HCl
5/2	130	5.45	47.5	0.053	0.56	0.64	1.14	*0.4 gr.Q.HCl
5/3	82	5.45	43.5	0.053	0.52	0.59	1.19	*0.6 gr.Q.HCl
"5/4								*0.6 gr.Q.HCl

The presence of feces in the urine probably accounts for the sudden change in reaction.

* The 0.4gr. and 0.6 gr. doses of quinine were divided into two and three portions respectively and administered at intervals of about three hours beginning at 8:00 A.M.

" The animal died on this date exhibiting the symptoms of the preceding one especially the marked pyloric stenosis

Table XII

Date	Urine vol.	P_H	Ttrble ac.cc.	Creat gr.	Urea & am.N gr.	Total N gr.	Body wt.kg.	Remarks
4/27	121	5.45	60.0	0.053	0.57	0.64	1.25	
4/28	114	5.45	61.0	0.060	0.58	0.66	1.25	
4/29							1.27	Urine lost giving stom. tube
4/30	136	5.92	44.0	0.061	0.55	0.62	1.24	
5/1	144	5.45	48.0	0.060	0.58	0.68	1.25	0.3 gr.Q.HCl
5/2	138	5.92	43.0	0.060	0.53	0.63	1.24	*0.4 gr.Q.HCl
5/3	102	6.63	32.5	0.060	0.53	0.63	1.26	*0.6 gr. Q.HCl
5/4	90	7.0	27.5	0.057	0.47	0.56	1.30	*0.6 gr.Q.HCl
5/5	160	5.45	35.5	0.065	0.50	0.58	1.25	
5/6	108	5.45	31.5	0.068	0.44	0.51	1.26	
5/7	106	5.45	28.0	0.062	0.47	0.53	1.25	
5/8	106	5.45	21.0	0.062	0.42	0.46	1.26	
5/9							1.25	Urine lost giving stom. tube.
5/10	120	6.23	24.0	0.062	0.42	0.46	1.26	
5/11	108	6.63	18.3	0.065	0.44	0.47	1.26	*0.8 gr.Q.HCl

The animal died on 5/12. Autopsy some time after death revealed a rupture of the stomach wall.

* The 0.4 gr. dose was divided into two portions and the 0.6 gr. and 0.8 gr. doses into three portions and administered at intervals of three to four hours beginning at 8:00 A.M.

Table X111

Date	Urine vol.	P_H	Ttrble ac.cc.	Creat. gr.	Urea & am.N gr.	Total N gr.	Body wt.kg.	Remarks
5/13	72	6.63	27.0	0.063	0.36	0.39	1.39	
5/14	86	6.63+	21.5	0.063	0.34	0.37	1.39	
5/15	110	#	#	0.062	0.32	0.36	1.40	
5/16	116	6.63	31.0	0.062	0.36	0.41	1.40	0.2 gr. Q.HCl
5/17	92	6.63	27.0	0.065	0.34	0.39	1.40	
5/18	124	6.63	23.0	0.063	0.35	0.41	1.40	
5/19	92	6.23	33.5	0.064	0.49	0.56	1.40	*0.4 gr. Q.HCl
5/20	110	6.23	28.0	0.075	0.43	0.49	1.40	
5/21	104	6.23	31.8	0.066	0.45	0.49	1.41	
5/22	66	6.63	26.0	0.066	0.41	0.46	1.40	*0.4 gr. Q.HCl

#A little milk was overturned in the cage and the reaction rendered abnormal.

*The 0.4 gr. doses of quinine were divided into two portions and given about four hours apart.

The animal died on May 23. Death was preceded by profuse salivation, loss of motor control and collapse. Autopsy immediately after death revealed the pyloric stenosis observed in the other animals. It was the intention to give the animal 0.6 gr. quinine on this date but after the administration of 0.4 gr. such marked symptoms of collapse were exhibited that no more was given.

The results of experiments to determine the effects of quinine on the nitrogen excretion in rabbits are not strictly confirmatory of the evidence obtained of this effect in the human organism. In cases where there was any lowering of the nitrogen excretion,which was never marked, it failed to rise again to the level of the preceding normal days hence it can not be stated that the effect was due to quinine alone. Some significance may be attached to the uniform autopsy finding of pyloric stenosis in the animals dying from the effects of the drug. It is possible that the mechanism for the discharge of the stomach contents into the intestine is disturbed. The hydrogen ion concentration and the creatinine elimination seem to be unaffected as was the case in the human organism.

Summary

(1) The literature has been reviewed to present the status of the question of the influence of quinine on the nitrogenous metabolism.

(2) The findings of the majority of former investigators in regard to the decrease in the urea and total nitrogen excretion in man under this condition have been confirmed. The evidence gained from experimental work on rabbits indicates that if the effect is similiar it is much less marked.

(3) The data of the experiments herein presented indicate that the effects of quinine on the uric acid elimination are slight. The results are certainly not in agreement with the profound decrease observed by Prior, von Noorden and Zuntz and others.

(4) The effects of quinine on the creatinine excretion have been investigated presumably for the first time in as much as no

reference was found in the literature. The creatinine elimination seems to be unappreciably effected.

(5) Quinine apparently exerts no influence on the hydrogen ion concentration of the urine.

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